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Abstract: Objective To explore the safety and efficacy of FFR-guided percutaneous coronary intervention (PCI) in vessels with severe diameter stenosis. Methods Results Of 1090 patients undergoing fractional flow reserve (FFR) assessment from 2002 to 2009, we identified 167 patients in whom FFR was measured in at least one 70%-89% stenotic lesion. These patients were subdivided into an FFR-defer group (= 49) if PCI was deferred (FFR > 0.80), and an FFR-perform group (= 118) if PCI was performed (FFR ≤ 0.80). Comparatively, an additional 1176 patients undergoing PCI in at least one lesion with 70%-89% stenosis but without measurement of FFR served as a control (angiography-guided) group. Clinical outcomes were compared during a median follow-up of 49.0 months. The 5-year Kaplan-Meier estimated revascularization rates were 16% in the FFR-defer group and 33% in the FFR-perform group (= 0.046). The incidence of major adverse cardiac events were comparable in these two groups (HR = 0.82, 95% CI: 0.37-1.82, = 0.63). The number of stents placed was significantly lower in the FFR-guided group (0.9 ± 0.8 vs 1.4 ± 0.8 , < 0.001). Conclusions Functional revascularization for lesions with visually severe stenosis is clinically safe and associated with fewer stents use. This study suggests that extending the use of FFR to more severe coronary lesions may be reasonable.

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Long-term outcomes after fractional flow reserve-guided percutaneous coronary intervention in patients with severe coronary stenosis

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Abstract

Objective To explore the safety and efficacy of FFR-guided percutaneous coronary intervention (PCI) in vessels with severe diameter stenosis. **Methods & Results** Of 1090 patients undergoing fractional flow reserve (FFR) assessment from 2002 to 2009, we identified 167 patients in whom FFR was measured in at least one 70%–89% stenotic lesion. These patients were subdivided into an FFR-defer group ($n = 49$) if PCI was deferred ($\text{FFR} > 0.80$), and an FFR-perform group ($n = 118$) if PCI was performed ($\text{FFR} \leq 0.80$). Comparatively, an additional 1176 patients undergoing PCI in at least one lesion with 70%–89% stenosis but without measurement of FFR served as a control (angiography-guided) group. Clinical outcomes were compared during a median follow-up of 49.0 months. The 5-year Kaplan-Meier estimated revascularization rates were 16% in the FFR-defer group and 33% in the FFR-perform group ($P = 0.046$). The incidence of major adverse cardiac events were comparable in these two groups ($\text{HR} = 0.82$, 95% CI: 0.37–1.82, $P = 0.63$). The number of stents placed was significantly lower in the FFR-guided group (0.9 ± 0.8 vs. 1.4 ± 0.8 , $P < 0.001$). **Conclusions** Functional revascularization for lesions with visually severe stenosis is clinically safe and associated with fewer stents use. This study suggests that extending the use of FFR to more severe coronary lesions may be reasonable.

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Keywords: Fractional flow reserve; Outcome; Percutaneous coronary intervention; Severe stenosis; Stent

1 Introduction

The benefits of percutaneous coronary intervention (PCI) are mainly attributable to the reduction of myocardial ischemia and symptoms,^[1] and this is reflected in clinical practice guidelines which presently recommend PCI only when symptoms and/or myocardial ischemia are present.^[2,3]

Historically, most studies of coronary revascularization have been based on angiographic criteria, and have defined a “significant” stenosis as $\geq 70\%$ diameter narrowing.^[2] In

current interventional practice, visual assessment of the angiographic reduction of luminal diameter remains the standard measure to gauge the severity of lesions. However, evidence has shown that coronary angiography frequently fails to accurately identify the hemodynamic significance of lesions.^[4,5]

Fractional flow reserve (FFR), based on coronary pressure measurements obtained during maximal hyperemia, has proven to be an accurate method to assess the functional significance of coronary stenosis.^[6] In the last decade, the reliability of FFR has been established in various clinical and anatomical subsets.^[7–17] In the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME 2 study, the decision-making to perform revascularization based on FFR leads to favorable clinical outcomes compared to conventional PCI or optimal medical therapy alone.^[18,19]

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Notably, more than half of the lesions in the FAME study were $> 71\%$ stenosis,^[20] and 20% of them had FFR greater than 0.80.^[21] Thus, the reliance on visual assessment has been questioned, and functional evaluation may be needed to identify the inducible ischemia for these angiographically severe lesions ($> 70\%$ diameter stenosis). Moreover, the baseline angiographic diameter stenosis has been reported to be associated with future myocardial infarction and major cardiac adverse events,^[22] and incomplete revascularization may result in a higher event rate.^[23] Therefore, the rationale for the use of FFR to evaluate severe stenosis is still uncertain, and the safety of deferring PCI for a severe lesion based on FFR is unclear.

The aim of this study is to preliminarily evaluate the usefulness of FFR-guided treatment strategy in patients with visually severe stenosis. We hypothesize that FFR-guide strategy is clinically reasonable.

2 Methods

2.1 Study population

A total of 1090 consecutive patients with use of FFR at the Mayo Clinic in Rochester, Minnesota between October 2002 and December 2009 were identified. Patients who underwent FFR measurement of at least one lesion with visual assessment of 70%–89% diameter stenosis were included in the FFR-guided group. These patients were further divided into: (1) those without subsequent PCI (FFR-defer group), and (2) those in whom PCI were performed following FFR measurement (FFR-perform group). Another, 6268 consecutive patients who received PCI without prior FFR measurements in the same time period were screened, and

only those undergoing PCI of at least one lesion with 70%–89% stenosis were included in the angiography-guided group (Figure 1). Because FFR was rarely used in lesions with 90%–99% stenosis, we did not include this subset of patients.

Patients were excluded from study analysis if they met any of the following exclusion criteria: (1) presentation with myocardial infarction in the prior 24 h or cardiogenic shock; (2) referral for coronary artery bypass surgery; (3) presence of left main disease; (4) FFR measurement and/or PCI in at least one lesion with stenosis $> 89\%$; (5) PCI of at least one vessel, with deferral of at least one other vessel after assessment of FFR; (6) $\text{FFR} \leq 0.80$ without PCI performed or PCI performance despite an $\text{FFR} > 0.80$; and (7) declined use of medical records for research purposes.

Medical records of all patients were reviewed to obtain information on clinical, laboratory and angiographic characteristics. The study was approved by the Institutional Review Board of the Mayo Clinic.

2.2 Intracoronary pressure measurements

Intracoronary pressure measurement was performed using a 0.014-inch pressure-monitoring guidewire (Pressure Wire, Radi Medical, Uppsala, Sweden, or Wave Wire, Volcano, Rancho Cordova, Calif). The pressure wire was introduced via a 5F, 6F or 7F guiding catheter, calibrated and advanced into the coronary artery distal to the assessed stenosis as described previously.^[6] Doses up to 72 μg of intracoronary adenosine were given to 1047 (96%) patients and intravenous adenosine at a rate of 140 $\mu\text{g}/\text{kg}/\text{min}$ were administered to 43 (4%) patients for achievement of maxi-

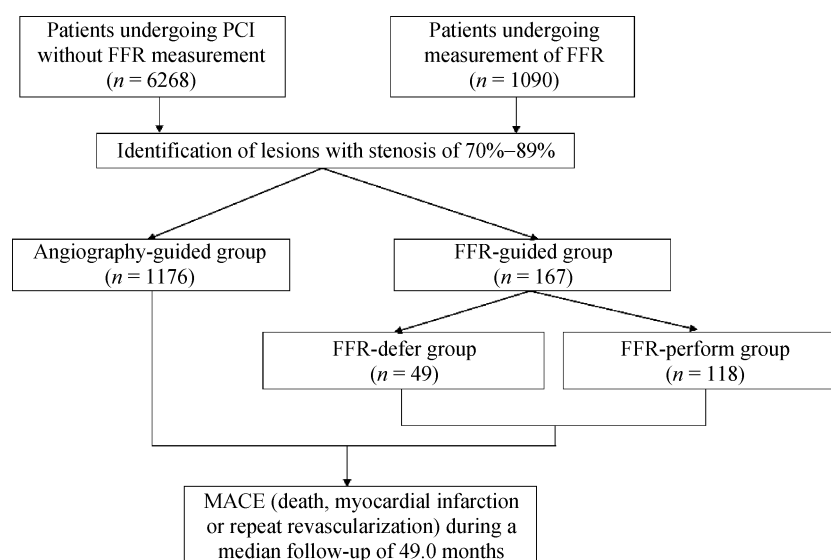


Figure 1. Study-flow chart. FFR: fractional flow reserve; MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

mal coronary blood flow. Fractional flow reserve was calculated as the ratio of the mean distal (trans stenotic) coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter at maximal hyperemia.^[24] The threshold to perform or defer PCI was based on FFR of 0.80.

2.3 Clinical follow-up

Patients with PCI were followed via telephone calls at 6 months, 12 months, and annually thereafter. Hospital records were reviewed to record follow-up events. Patients with deferred PCI were contacted via a single questionnaire and chart review.

Clinical outcomes were compared between the FFR-perform and FFR-defer groups, and between the FFR-guided and angiography-guided groups. The primary endpoint was major adverse cardiac events (MACE), defined as composite of death, myocardial infarction (MI) or any revascularization. The secondary endpoints were the individual components of MACE and the number of stents placed per patient. Death was all-cause mortality. MI was defined when two of the following three criteria were met: (1) prolonged chest pain > 20 minutes; (2) cardiac biomarker elevation > 2 times normal limit; and (3) ST-T segment changes or new Q waves on serial electrocardiogram indicative of myocardial damage.^[25] Revascularization was defined as any clinically driven revascularization including bypass surgery.

2.4 Statistical analysis

Continuous variables are summarized as mean \pm SD for most variables, or median (25th, 75th percentile) where indicated. Discrete variables are summarized as frequency (group percentage). Group comparisons are tested using Student's two-sample *t*-test for most continuous variables, the rank sum test for FFR measurement comparisons, and Pearson's chi-squared test for discrete data. Kaplan-Meier estimates were used to estimate survival curves, with the log-rank test employed to test differences between groups. Cox proportional hazards multiple regression models were used to estimate the association between FFR use and deferral on long-term outcomes after adjusting for age, gender, body mass index, hypertension, high cholesterol, smoking status, diabetes, ejection fraction. These covariates were chosen based on clinical relevance. All significance tests were two-tailed with a 0.05 significance level. All analyses were conducted using SAS 9.2 (SAS Institute, Cary NC).

3 Results

3.1 Baseline characteristics

In the FFR-guided group, 49 (29%) patients were deferred

PCI (FFR-defer group) and 118 (71%) patients ultimately underwent PCI after FFR assessment (FFR-perform group). Patients in the former group were older and with lower prevalence of hypercholesterolemia. A total of 1176 patients were included in the angiography-guided group. The average number of stents placed was 0.9 ± 0.8 per patient in the FFR-guided and 1.4 ± 0.8 per patient in the angiography-guided group ($P < 0.001$). More patients undergoing PCI received dual anti-platelet therapy on discharge. Clinical and angiographic characteristics of the each group are shown in Tables 1 & 2. In-hospital events are shown in Table 3.

3.2 Follow-up

Clinical events were collected during a median follow-up of 49.0 months (Q1, Q3: 23.0, 70.0). Length of follow-up was 39.8 (25.9, 72.6) months in the FFR-defer and 46.3 (21.7, 65.3) months in the FFR-perform group ($P = 0.68$). The length of follow-up in the FFR-guided was 46.2 (24.0, 65.9) months and 50.2 (22.9, 70.3) months in the angiography-guided group ($P = 0.08$). The rate of follow-up was 94% in the FFR-guided group and 97% the angiography-guided group.

3.3 Long-term outcomes between the FFR-defer and FFR-perform groups

The 5-year Kaplan-Meier estimated event rates for MACE (28% vs. 41%, $P = 0.18$), mortality (13% vs. 10%, $P = 0.44$), MI (7% vs. 10%, $P = 0.52$), mortality or MI (20% vs. 19%, $P = 0.73$), and mortality or revascularization (28% vs. 40%, $P = 0.22$) were similar between the FFR-defer and FFR-perform groups, respectively (Figure 2). The revascularization rate over 5 years was significantly lower in the FFR-defer group compared to the FFR-perform group (16% vs. 33%, $P = 0.046$).

After adjustment for age, sex, body mass index, incidence of hypertension, hypercholesterolemia, smoking, diabetes, and left ventricular ejection fraction in a Cox multivariable model, the deferral of PCI based on $\text{FFR} > 0.80$ did not increase the incidence of MACE (HR = 0.82, 95% CI: 0.37–1.82, $P = 0.63$) or its component elements (Table 4).

3.4 Long-term outcomes in the FFR-guided and angiography-guided groups

The 5-year Kaplan-Meier event rates for MACE were 37% and 38% ($P = 0.83$), mortality 11% and 18% ($P = 0.07$), MI 9% and 8% ($P > 0.99$), mortality or MI 19% and 24% ($P = 0.18$), revascularization 28% and 22% ($P = 0.12$), mortality or revascularization 36% and 37% ($P = 0.78$) in the

Table 1. Baseline characteristics of patients.

Variables	Angiography-guided group (n = 1176)	FFR-guided group (n = 167)		
		All (n = 167)	FFR-defer (n = 49)	FFR-perform (n = 118)
Age, yrs	67.0 ± 11.7	65.2 ± 11.5	68.0 ± 10.9 [‡]	64.1 ± 11.7
Male gender	746 (63.4%)	114 (68.3%)	29 (59.2%)	85 (72.0%)
Body mass index	30.1 ± 6.2	30.9 ± 5.9	31.2 ± 6.2	30.7 ± 5.8
Current smoking	117 (9.9%)	24 (14.4%)	4 (8.2%)	20 (17.0%)
Diabetes mellitus	326 (27.7%)	49 (29.3%)	15 (30.6%)	34 (28.8%)
Hypertension	902 (76.7%) [§]	143 (85.6%)	43 (87.8%)	100 (84.7%)
Hypercholesterolemia	918 (78.1%) [*]	116 (69.5%)	17 (35.0%) [†]	99 (84.0%)
Angina (CCS III–IV)	547 (46.5%)	80 (47.9%)	18 (36.7%)	62 (52.5%)
History of MI (> 7 days)	265 (22.5%)	40 (24.0%)	11 (22.4%)	29 (24.6%)
Prior PCI	349 (29.7%) [*]	74 (44.3%)	22 (44.9%)	52 (44.1%)
History of CHF	143 (12.1%) [§]	31 (18.6%)	10 (20.4%)	21 (17.8%)
CVD	109 (9.3%)	13 (7.9%)	6 (12.2%)	7 (5.9%)
PAD	117 (9.9%)	16 (9.6%)	5 (10.2%)	11 (9.3%)
COPD	142 (12.1%)	13 (7.9%)	4 (8.2%)	9 (7.6%)
Renal dysfunction	58 (4.9%)	5 (3.0%)	2 (4.1%)	3 (2.5%)
LVEF ≤ 40%	100 (8.5%)	15 (9.0%)	5 (10.2%)	10 (8.5%)
Aspirin on discharge	1135 (96.5%) [§]	153 (91.6%)	43 (87.8%)	110 (93.2%)
Clopidogrel on discharge	1151 (97.9%) [*]	128 (76.6%)	13 (26.5%) [†]	115 (97.5%)
Beta-blockers on discharge	903 (76.8%)	130 (77.8%)	37 (75.5%)	93 (78.8%)
Calcium channel blocker on discharge	208 (17.7%)	35 (21.0%)	8 (16.3%)	27 (22.9%)
ACE inhibitors on discharge	677 (57.6%)	92 (55.1%)	22 (44.9%)	70 (59.3%)
Lipid lowering drugs on discharge	592 (50.3%) [*]	102 (61.1%)	38 (77.6%) [†]	64 (54.2%)

Data are presented as means ± SD or n (%). [§]P < 0.05 as compared to FFR-guided group; ^{*}P < 0.001 as compared to FFR-guided group; [†]P < 0.05 as compared to FFR-perform group; [†]P < 0.001 as compared to FFR-perform group. CCS: Canadian Cardiovascular Society; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CVD: cerebral vascular disease; FFR: fractional flow reserve; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention.

Table 2. Angiography and PCI characteristics.

Variables	Angiography-guided group (n = 1176)	FFR-guided group (n = 167)		
		All (n = 167)	FFR-defer (n = 49)	FFR-perform (n = 118)
LAD stenosis ≥ 70%	697 (59.3%) [§]	113 (67.7%)	25 (51.0%) [†]	88 (74.6%)
LCX stenosis ≥ 70%	329 (30.0%)	38 (22.6%)	15 (30.6%) [†]	23 (19.5%)
RCA stenosis ≥ 70%	423 (36.0%)	41 (24.6%)	13 (26.5%)	28 (23.7%)
FFR in LAD	--	118 (70.7%)	32 (65.3%)	86 (72.9%)
FFR in LCX	--	22 (13.2%)	9 (18.4%)	13 (11.0%)
FFR in RCA	--	30 (18.1%)	10 (20.4%)	20 (16.9%)
Median FFR value (Q1, Q3)	--	0.77 (0.70, 0.82)	0.88 (0.83, 0.91) [†]	0.74 (0.68, 0.77)
PCI in native LAD	660 (56.1%)	88 (50.9%)	--	88 (74.6%)
PCI in native LCX	284 (24.1%) [*]	17 (10.2%)	--	17 (14.4%)
PCI in native RCA	396 (33.7%) [*]	22 (13.4%)	--	26 (22.0%)
Number of vessel treated				
1	1023 (87.0%)	105 (63.0%)	--	105 (89.0%)
2	146 (12.4%)	13 (7.8%)	--	13 (11.0%)
3	4 (0.3%)	0	--	0
Number of stents placed	1.4 ± 0.8 [*]	0.9 ± 0.8	--	1.3 ± 0.7
Procedural success of stents placement	1161 (98.7%)	--	--	117 (99.2%)

Data are presented as means ± SD or n (%). [§]P < 0.05 as compared to FFR-guided group; ^{*}P < 0.001 as compared to FFR-guided group; [†]P < 0.05 as compared to FFR-perform group; [†]P < 0.001 as compared to FFR-perform group. FFR: fractional flow reserve; LAD: left anterior descending; LCX: left circumflex; PCI: percutaneous coronary intervention; RCA: right coronary artery.

Table 3. In-hospital events.

Variables	Angiography-guided group (n = 1176)	FFR-guided group (n = 167)		
		All (n = 167)	FFR-defer (n = 49)	FFR-perform (n = 118)
Death	0	0	0	0
Death/Q-wave MI/stroke/CABG	2 (0.2%)	0	0	0
Q-wave MI	0	0	0	0
Emergency CABG	0	0	0	0
In-hospital CVD	2 (0.2%)	0	0	0
In-hospital any MI	41 (3.5%)	6 (3.4%)	0	6 (5.1%)

Data are presented as n (%). CABG: coronary artery bypass grafting; CVD: cerebral vascular disease; FFR: fractional flow reserve; MI: myocardial infarction.

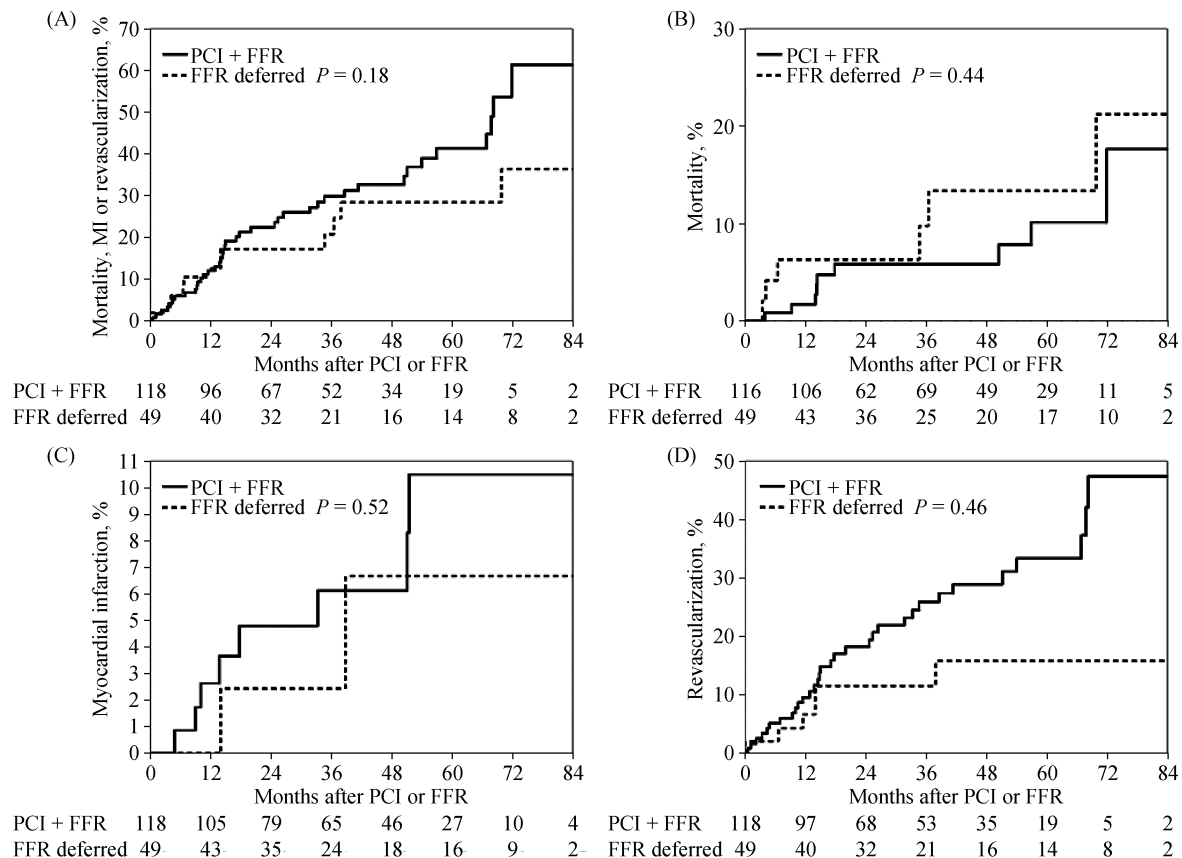


Figure 2. Long-term adverse events in FFR-defer group vs. FFR-perform group. (A): Kaplan-Meier curves for MACE during follow-up; (B): Kaplan-Meier curves for death during follow-up; (C): Kaplan-Meier curves for myocardial infarction during follow-up; and (D): Kaplan-Meier curves for revascularization during follow-up. FFR: fractional flow reserve; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention.

FFR-guided group and the angiography-guided group, respectively (Figure 3). In the Cox multivariable model, no differences in the risk of outcome events between groups (Table 4).

4 Discussion

In this study, when FFR was used to assess the functional significance in lesions with 70%–89% stenosis, PCI was de-

ferred in almost one third of patients. Importantly, their incidence of MACE was lower compared to those undergoing PCI although this was only statistically significant for the endpoint of repeat revascularization, indicating that deferral of PCI based on FFR > 0.80 is clinically safe. Compared to conventional PCI, the FFR-guided treatment strategy was associated with a significantly lower number of stents placed.

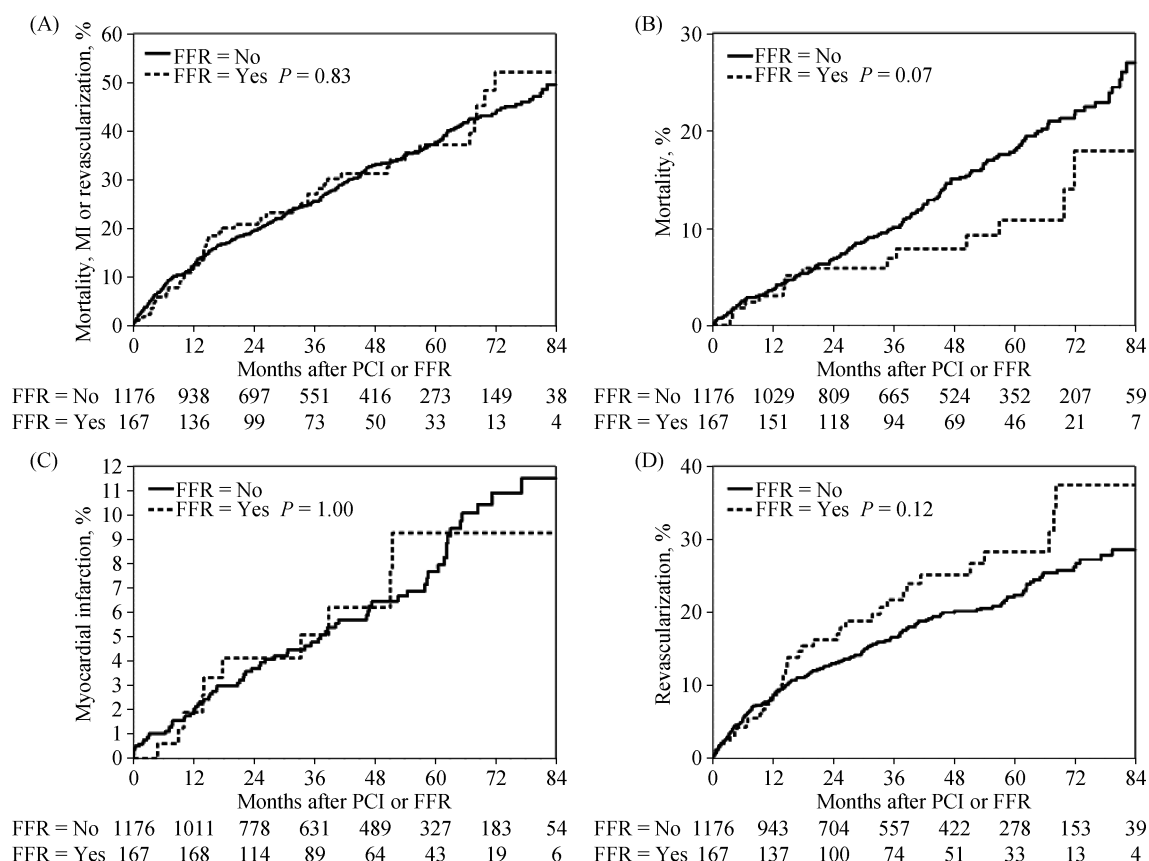


Figure 3. Long-term adverse events in FFR-defer group vs. angiography-guided group. (A): Kaplan-Meier curves for MACE during follow-up; (B): Kaplan-Meier curves for death during follow-up; (C): Kaplan-Meier curves for myocardial infarction during follow-up; and (D): Kaplan-Meier curves for revascularization during follow-up. FFR: fractional flow reserve; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention.

Table 4. Cox multivariable models to identify hazard ratio of outcome events.

Events	Adjusted* HR	95% CI	P-value
Deferred PCI after FFR vs. Perform PCI			
MACE	0.82	0.37–1.82	0.63
Revascularization	0.51	0.18–1.45	0.20
Mortality or Revascularization	0.85	0.38–1.91	0.70
Mortality or Myocardial infarction	1.60	0.53–4.89	0.41
FFR use vs. no FFR			
MACE	1.06	0.79–1.43	0.69
Mortality	0.67	0.39–1.14	0.14
Mortality or Revascularization	1.07	0.79–1.43	0.70
Mortality or Myocardial infarction	0.83	0.54–1.27	0.39

*Adjusted for age, sex, body mass index, smoking history, diabetes, hypertension, hypercholesterolemia, left ventricular ejection fraction. FFR: fractional flow reserve; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention.

Although the FAME study suggests that angiography is inaccurate in assessing functional significance for both intermediate and severe stenoses, no further investigation has been conducted to explore the rationale for the use of FFR in lesions of $\geq 70\%$ stenosis.^[21] Moreover, the role of di-

ameter narrowing severity in predicting future events has been demonstrated in previous studies.^[22,26] When using the residual SYNTAX score based on angiographic appearance to quantify and risk-stratify the degree and complexity of residual stenosis after PCI, incomplete revascularization is

associated with a worse prognosis compared with complete revascularization.^[23] Hannan, *et al.*^[27] reported that incomplete revascularization was associated with suboptimal long-term outcome. Therefore, the safety of deferring PCI in a functionally non-significant, but angiographically severe lesion is still a potential concern. However, the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) has reported no difference in outcomes between PCI plus optimal medical therapy and optimal medical therapy alone in patients with over 70% stenosis.^[28] As is known, angiography only depicts coronary anatomy from a planar two-dimensional silhouette of the lumen, and provides little characterization of plaque morphology or vessel wall, both of which play an important role in plaque destabilization.^[29] In the recent PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), a small luminal area and large plaque burden measured by intravascular ultrasound were significant predictors of subsequent events, but there was no relationship between stenotic severity on conventional angiography and prognosis.^[30] The current study, to our knowledge, firstly demonstrated that deferral of PCI based on FFR resulted in similar, if not improved, long-term outcomes compared to performing PCI, underscoring the safety of an FFR-guided approach.

The incidence of 5-year repeat revascularization was 16% in the FFR-defer group, which was significantly lower than that in the FFR-perform group (33%). A similar conclusion has been reported in the FAME study,^[20] where only one third of repeat revascularizations during follow-up were related to the originally deferred lesions. In the DEFER study (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis), even when treated by PCI, the chance of adverse events related to a functionally significant stenosis in the next 5 years was several times higher than for a stenosis of similar angiographic severity but not associated with reversible ischemia and treated medically.^[12] Importantly, in the current study, the difference in the rates of repeat revascularization between the FFR-defer and FFR-perform groups appeared after 13 months of the index procedure, and became more significant over time, which indicating that this benefit mainly derives from fewer late or very late adverse events, and not from reduction of periprocedural complications.

Of those lesions considered angiographically severe, the vast majority are hemodynamically significant, therefore routine use of FFR will likely be controversial given the associated costs.^[31] In this study, the FFR-guided group was

associated with fewer stents placed. Considering that the pressure wire is applicable for PCI after measurement of FFR, in addition to lower amount of contrast media and dual anti-platelet therapy, functional revascularization should be more economic. Furthermore, Fearon, *et al.*^[32] reported that 30% of the overall cost benefits of FFR-guided treatment strategy was generated during follow-up. In our study, fewer repeat revascularizations in the next five years may lead to further cost savings after the initial procedure.

In the current study, the difference in outcomes between the FFR-guided and angiography-guided groups was not as significant as shown in the FAME study.^[20] This may mainly be attributable to the relatively higher proportion of functionally severe lesions in this stenosis subset compared to the intermediate stenosis.

4.1 Limitation

This is a single-center, observational study. Small sample size and its retrospective design limit the statistical power and strength of the conclusions. It was performed in a non-selected population of everyday practice with differences in baseline characteristics. Multiple regression analysis may mitigate bias after adjustment of confounding factors, but unmeasured indicators of FFR use leave room for residual bias.

PCI patients are followed regularly by telephone as standard clinical practice, but FFR patients who did not have any PCI performed had their follow-up information collected via a questionnaire and history review. Events outside our institution may have been missed in FFR patients who did not return their questionnaire. On the other hand, healthy patients with no events who did not return to Mayo may have been excluded for lack of follow-up.

96% of the patients received escalating doses of adenosine up to 72 μ g in this study until maximal hyperemia and the lowest FFR were achieved. Nevertheless, some studies reported that an intracoronary bolus dose > 300 μ g could be equal to or more effective in achieving maximum hyperemia when calculating the FFR. Therefore, the dose of intracoronary adenosine used in this study might be too low, resulting in misclassification for some patients.

4.2 Conclusion

The FFR-guided strategy is safe to include in the decision making process for PCI in patients with severe stenosis. This study extends the validation of functional assessment-based revascularization to more severe coronary lesions. Randomized, controlled studies with large sample size are needed to confirm our preliminary findings.

Acknowledgments

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